201-16057

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Administrator
U.S. Environmental Protection Agency
Ariel Rios Building
Room 3000, #1101-A
1200 Pennsylvania Avenue N.W.
Washington, D.C. 20460

October 24, 2005

Dear Administrator:

On behalf of the Eastman Chemical Company, I wish to thank the Environmental Protection Agency (EPA) for their comments on the test plan and robust summaries on the substance recognized as methyl 4-formylbenzoate. Eastman Chemical Company has sponsored the collection of hazard data and is responsible to coordinate testing activities for this substance under the Chemical Right-to-Know Program. Eastman Chemical Company has supported the collection and review of available test data and the development of test plans and robust summaries.

Based on our initial recommendations in the test plan and the peer-reviewed comments of the EPA, I am pleased to submit the following revised test plan and robust summaries for the methyl 4-formylbenzoate. The revised test plan and robust summaries contain additional physical and chemical data and information that addresses the questions and comments made by the EPA in its letter dated 1/14/2004. The letter being submitted now contains responses to the specific comments made by the EPA. These responses taken together with the inclusion of new data and other information constitute the key changes to the original test plan and robust summaries.

Based on this additional information, it is concluded that the experimental and model data for physiochemical properties, environmental fate, ecotoxicity, and human health endpoints are consistent for this substance. The database of information permits one to reliably predict endpoint values for this substance and other structurally related substances.

The EPA comprehensive comments provided the necessary guidance to complete the test plan for this category. The collaboration between the Eastman Chemical Company and the Environmental Protection Agency in the Chemical "Right to Know" Program has produced

a hazard database that will be useful to the public for decades to come. Thank you for the opportunity to participate in such a program.

If you have any questions or comments concerning the contents of this letter, please feel free to contact me at any time (202-331-2325) or tadams@therobertsgroup.net.

Best regards,

Timothy B. Adams, Ph.D.
Technical Contact Person for Eastman Chemical Company

EPA Comments on Chemical RTK HPV Challenge Submission:
Methyl 4-Formylbenzoate

Summary of EPA Comments

The sponsor, Eastman Chemical Company, submitted a test plan and robust summaries to EPA for methyl 4-formylbenzoate, CAS No. 1571-08-0 on July 27, 2003. EPA posted the submission on the ChemRTK HPV Challenge Web site on August 19, 2003. Information was also provided for several analogs: terephthalic acid, benzaldehyde, methyl benzoate, and dimethyl terephthalate.

EPA has reviewed this submission and has reached the following conclusions:

1. **Analog Justification.** EPA agrees with the submitter's analogs for the health effects endpoints and, with the exception of terephthalic acid, for the ecological effects endpoints.

2. **Physicochemical Properties.** The submitter needs to provide measured vapor pressure and water solubility data.

Based on the observations that the EPIWIN calculated value (0.00088kPa) for methyl 4-formylbenzoate is in the same order of magnitude (0.00133 kPa) as that for dimethyl terephthalate and the only difference between the two molecules is that, in one case, methyl benzoate contains a *p*-aldehyde function while in the other methyl benzoate contains a *p*-methyl ester function, it is concluded that the calculated value adequately reflects the measured value of vapor pressure for methyl 4-formylbenzoate.

Based on the water solubility value (37.2 mg/L) for the structurally related substance dimethyl terephthalate and terephthalic acid (19 mg/L) at 25 °C, the calculated water solubility (3136 mg/L) of methyl 4-formylbenzoate is two orders of magnitude higher. The water solubility of this substance should be in the same range as the corresponding acid (terephthalic acid) and methyl ester derivative (dimethyl terephthalate).

3. **Environmental Fate.** The submitter needs to include the input values used in its fugacity model in the robust summary. EPA recommends that the submitter use the Level III model instead of the level I model for the fugacity calculation. The submitter needs to address some deficiencies in the biodegradation robust summary.

The Level III fugacity model has been used to recalculate transport in the environment. The revised robust summary has been included in the revision. Additional biodegradation data has been included in the revised robust summary, if available in the original reports.

4. **Health Effects.** All endpoints have been adequately addressed for the purposes of the HPV Challenge Program.

5. **Ecological Effects.** All endpoints have been adequately addressed for the purposes of the HPV Challenge Program.

EPA Comments on the Methyl 4-formylbenzoate Challenge Submission

Analog Justification

EPA agrees with the submitted analogs for methyl 4-formylbenzoate for the health effects endpoints. In general, the presentation was unfocused and too long. For example, information on hydrolysis at an acidic pH was omitted although measured data were evidently available in the reference cited (Hoffman, 2003). The most relevant data in a series of hydrolysis experiments on alkyl benzoates, the plasma half-lives for methyl benzoate, were not included, yet, it appears that they were reported in Nielson and Bundgaard (1987). In general, the information provided on hydrolysis, especially under conditions found in gastric juice, is poorly addressed. Important questions about the rate of hydrolysis remain unanswered.

The hydrolysis data at pH=4 and 9 have been added to the appropriate robust summary. In addition, a robust summary for the human plasma hydrolysis of methyl benzoate has been prepared.

Most of the analog information supplied was considered relevant for ecological effects endpoints. Terephthalic acid data were not considered suitable for the following reasons:
• The submitter reported that the estimated half-life at pH 7 and 25 °C was 3286 hours (136.9 days; p.14, robust summary) for methyl 4-formylbenzoate, which suggests that significant hydrolysis of the ester to the acid is not likely to occur under the conditions of an acute aquatic toxicity test.

The half-life of 3286 hours was extrapolated from hydrolysis data in simple aqueous solutions (pH=7) over a range of temperatures. As such it does not reflect rates of hydrolysis in either aquatic species or animals. Additional data has been added to the test plan for the hydrolysis of methyl benzoate in fish species and in human plasma. These data indicate that the benzoate ester is rapidly hydrolyzed *in vivo*.

• Acids such as terephthalic acid become charged species under the conditions of aquatic toxicity testing, with different toxicological behavior from esters such as dimethyl terephthalate and methyl 4-formylbenzoate.

Test Plan

Physicochemical Properties (*melting point, boiling point, vapor pressure, partition coefficient and water solubility*)

The data provided by the submitter for melting point, boiling point, and partition coefficient are adequate for the purposes of the HPV Challenge Program.

Vapor pressure. The data provided by the submitter are not adequate for the purposes of the HPV Challenge Program. The submitter estimated a vapor pressure of 0.88 Pa at 25 ° C using MPBPVP v1.40. According to HPV Guidelines, vapor pressures estimated to be $>10^{-5}$ Pa ($>7.5x10^{-8}$ mm Hg) need to be measured (OECD TG 104). Data provided for related chemicals dimethyl terephthalate, methyl benzoate and benzaldehyde suggest that the vapor pressure of methyl 4-formylbenzoate is greater than 10^{-5} Pa. The submitter needs to provide measured data for methyl 4-formylbenzoate following OECD guidelines. Measured data from published sources are acceptable, as long as the submitter identifies the reference.

Although we agree that the vapor pressure of methyl 4-formylbenzoate is > 10^{-5}, we contend that the measured vapor pressure of dimethyl terephthalate closely approximates that for methyl 4-formybenzoate (refer to discussion of vapor pressure above). The HPV Guidelines are not rigid rules but guidelines to be followed in the absence of data. There is sufficient data on structural analogs to justify not performing additional studies on this endpoint. These data structural analogs is permitted according to the EPA guideline document titled The Use of Structure-activity Relationships in the High Production Volume

Chemical "Right to Know" Program. In that document is noted that "in the event that neither measured data or reference book values are available, estimations using an appropriate model will be accepted for all the physiochemical endpoints".

Water solubility. The submitter estimated a water solubility of 3,136 mg/L at 25 ° C using WSKOW v1.40. Estimated water solubility values are generally not acceptable for the purposes of the HPV Challenge Program. The submitter provided water solubility data for two structural analogs: 15 mg/L at 10 ° C and 19 mg/L at 25 ° C for terephthalic acid, and 28.7 mg/L at 20 ° C and 37.2 mg/L at 25 ° C for dimethyl terephthalate. These data suggest that methyl 4-formylbenzoate will have a water solubility on the order of 20 mg/L. Since the water solubility estimate is >1 μg/L, the submitter needs to provide measured water solubility data for methyl 4-formylbenzoate following OECD TG 105. Measured data from published sources are acceptable, as long as the submitter identifies the reference.

The submitter agrees with EPA, that the water solubility of methyl 4-formylbenzoate is approximately 20 mg/L. Based on the data for structural analogs, it is unnecessary to generate addition data that is anticipated to have little impact on the hazard determination of this substance.

Environmental Fate (*photodegradation, stability in water, biodegradation, fugacity*)

The data provided by the submitter for photodegradation, stability in water, and biodegradation are adequate for the purposes of the HPV Challenge Program.

Fugacity. The sponsor estimated the fugacity of these chemicals using a level I model. Although EPA had previously recommended level I, this model is somewhat limited. EPA now recommends the use of level III, which provides a more rigorous level of analysis. EPA believes that values based on a level III fugacity model are more realistic and useful for estimating a chemical's fate in the environment. The submitter needs to recalculate its fugacity model using measured water solubility and vapor pressure data, and to incorporate in the robust summary all input values used.

Level III fugacity calculations have been performed and the data incorporated into the robust summaries section.

Health Effects (*acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity*)

Adequate data are available to satisfy the acute, repeated-dose, genetic, and reproductive/developmental toxicity endpoints. With the exception of acute toxicity, EPA agrees with the reliance on information provided by analogs. The submitter needs to address a few deficiencies in the robust summaries.

Ecological Effects *(fish, invertebrates, and algae*)

Data for dimethyl terephthalate and methyl benzoate are adequate to satisfy the endpoint for fish, data for dimethyl terephthalate, methyl benzoate, and benzaldehyde for invertebrates, and data for dimethyl terephthalate and benzaldehyde for algae.

Specific Comments on the Robust Summaries

Generic comments

The format for reporting information from individual studies is misleading. The "header" for each study identifies the sponsored HPV chemical and is followed with a CAS No. for that chemical. However, there is no indication in the header whether the summary that follows is on the HPV

chemical or an analog. The identity of the test substance is often provided in a "remarks" section but this format is variable (see pages 90 and 91 of the robust summaries) and in some cases, the reader does not find out until the end of the summary that the test substance used was not the HPV chemical. On page 96, the test substance is unclear since two chemicals are identified in the summary; however, this study is coded as unreliable and could be omitted.

The "remarks for substance" section has been made consistent such that the reader can identify the substance tested in that section of each robust summary. The robust summary on Page 96 has been changed to properly identify the test substance.

A citation for the WHO document (Technical Information Series, 2001) referred to on p. 25 was omitted in the list of references and should be added.

This reference has been added to the test plan.

Environmental Fate (*photodegradation, stability in water, biodegradation, fugacity*)

Biodegradation. The submitter needs to provide information on the purity of the substance and total contact time in its biodegradation robust summary for methyl 4-formylbenzoate.

Additional data were added to the robust summary if available in the original report.

Health Effects

All summaries for health effects studies were missing the purity of the test material and the CAS Nos. for analogs.

Developmental Toxicity. A robust summary for a developmental toxicity assay in rats exposed to particulate terephthalic acid by inhalation on gestational days 6-15 was missing information on the test atmosphere, including the particle size distribution and the relationship of the highest tested concentration to the highest attainable concentration.

Additional data were added to the robust summary if available in the original report.

Ecological Effects

Fish. Information missing from one or more of the robust summaries of acute toxicity of dimethyl terephthalate, methyl benzoate, and benzaldehyde to fish included test substance purity, test type, concentrations tested/responses, fish specifications, water quality parameters, control /response, statistical methods used, and whether or not the reported LC_{50} values were based upon measured or nominal concentrations.

The robust summaries for the studies of methyl benzoate in *Lepomis macrochirus* reported that "Undissolved test substance was noted at the two highest concentrations." The submitter needs to discuss the potential mechanisms for the formation of the salt/undissolved test substance and whether or not valid aquatic toxicity studies can be conducted in the absence of analytical monitoring in light of the fact that no water solubility data were reported. The submitter also needs to discuss whether or not the presence of undissolved test substance at 40 and 80 mg/L may have affected the derivation of the LC50 value since the test substances may have reacted with other components of the test systems, resulting in reduced concentrations of the test compounds over the course of these aquatic studies.

Additional data were added to the robust summaries if available in the original reports. A discussion of the effect of undissolved test substance on the LC50 value has been included in the robust summary. The undissolved substance may have affected lethality and LC50 determinations. However, no deaths were observed at 10 and 20 mg/L, levels

at which the substance is anticipated to be soluble. Therefore, the LC50 should exceed 20 mg/L.

Invertebrates. Information missing from one or more of the robust summaries of acute toxicity of dimethyl terephthalate, methyl benzoate, and benzaldehyde to *Daphnia magna* included test substance purity, duration of exposure, concentrations tested/responses, control/response, animal specifications, water quality parameters, statistical methods used, and whether or not the reported EC50 values were based upon measured or nominal concentrations.

Algae. Information missing from one or more of the robust summaries of acute toxicity of dimethyl terephthalate, and benzaldehyde to green algae included test substance purity, effects seen at each concentration tested (e.g., whether or not the identified growth inhibition took place at the highest concentration), control/response, statistical methods used, and whether or not the reported EC_{50} values were based upon measured or nominal concentrations and the submitter needs to provide a 72-hr EC_{50} value.

Additional data were added to the robust summaries if available in the original report.